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ORIGINAL ARTICLE

Informing family members of individuals with Lynch syndrome: a guideline for clinical geneticists

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Abstract The diagnosis of Lynch syndrome can lead to the prevention of colorectal cancer through periodic colonoscopies and removal of premalignant lesions in susceptible individuals. Therefore, predisposed individuals identified by mutation analysis are advised to inform their at-risk relatives about the options of predictive DNA testing and preventive measures. However, it has now been established that more than half of these relatives do not receive the necessary information. Barriers in conveying information include family communication problems and variable attitudes and practice among clinical geneticists. In this complex field, both medical, psychological, ethical and juridical aspects deserve consideration. Here we summarize the development of a revised guideline for clinical geneticists that allows a more active role of the geneticist, aimed at improving procedures to inform family members in Lynch syndrome and other hereditary and familial cancer syndromes.

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Introduction

While the individual doctor–patient relationship is a central theme in medicine, the family is of unique importance in the field of clinical genetics. Not only is the family history essential for diagnostic purposes, the outcome of the diagnostic process is often highly relevant for multiple family members. Pedigree data may show, for example, early-onset colorectal cancer in successive generations, suggesting Lynch syndrome, an autosomal dominant condition due to germline mutations in DNA mismatch repair (MMR) genes. The individual who applies for genetic counselling may be a patient with a current or past cancer

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history or a healthy relative. For confirmation of family history data, the counselee will often be asked to contact relatives and request their consent for the collection of medical data. If Lynch syndrome is suspected, the next diagnostic step is DNA testing, which is preferably performed in an individual with a current or past cancer history. This could be, for example, the brother of a healthy individual who has applied for genetic counselling. In suspected Lynch syndrome, DNA testing is usually preceded by a test on tumour tissue for markers of an MMR defect. Subsequently, DNA testing for the detection of a germline defect is performed on a blood sample from the patient whose tumour has shown a probable MMR defect. Both assays are preceded by an informed consent procedure. If the DNA test confirms the diagnosis of Lynch syndrome, a healthy relative can undergo presymptomatic DNA testing, which will show whether this individual is a carrier of the familial mutation or not. If the genetic predisposition for colorectal cancer is identified, the unaffected mutation carrier will be advised to undergo 2-yearly colonoscopies aimed at identifying and removing precancerous colorectal adenomas. For female mutation carriers, gynaecological surveillance will also be advised due to a high endometrial cancer risk. Preventive measures for the early detection of other types of tumours may also be recommended. It has now been established that regular monitoring of individuals from Lynch syndrome families leads to reduction in colorectal cancer mortality [1].

In Lynch syndrome, due to the autosomal dominant inheritance pattern, the pedigree data will often show multiple family members at risk of carrying the familial cancer predisposition. In the example mentioned of a healthy counselee with an affected brother, these family members include other siblings of the counselee, the children of the affected brother, and multiple family members in the paternal or maternal branch of the family, depending on the side of the family from which the deleterious mutation has been inherited. For all these at-risk family members, the information that Lynch syndrome has been diagnosed is highly relevant for the prevention or early detection and treatment of disease. In addition, if the mutation is detected in a particular family member, his or her children can now also undergo DNA testing and mutation carriers can start periodic colonoscopies at the recommended age of 25 years.

In the Netherlands, procedures to inform relatives of patients with Lynch syndrome and other hereditary conditions were established in 2007 as part of a general guideline on predictive DNA testing drawn up by the Dutch Society for Clinical Genetics [2]. In this guideline, two main principles were defined: (1) the issue of informing family members should be part of the genetic counselling process, and (2) the information to family members should be given by the counselee and not directly by the clinical geneticist. The geneticist should support the communication process by providing concise written information. The situation in which the counselee is not willing to contact family members was also addressed through options for direct contact by the clinical geneticist. These guidelines are in line with international recommendations, which will be summarized in the short literature review given below.

However, it has now become apparent that in practice these recommendations largely fail to achieve their goal. In fact, following current procedures, the majority of at-risk family members do not receive adequate information.

It was this apparent failure of current procedures that prompted the review of current practice and a reconsideration of the options for improving the information process in hereditary and familial cancer syndromes. The new guideline to be discussed in this article was developed on behalf of the Dutch Society for Clinical Genetics. The subject of informing relatives is not only relevant for Lynch syndrome but also for other hereditary and familial cancer families. In addition, the issues raised are relevant in many other fields of genetics, including cardiogenetics [3] and neuromuscular disease [4].

Methods

A multidisciplinary working group was established in which the disciplines of clinical genetics, medical psychology, health law and medical ethics were represented. As a first step current literature data were reviewed. Additional information was obtained by performing a survey among clinical geneticists and telephone interviews with patients and family members. Draft recommendations based upon these data were sent out for comments to the Dutch Society for Psychosocial Oncology (NVPO) and the Association of Cooperating Parent and Patient Organisations (VSOP).

For the literature review, the PubMed, Medline and PsychInfo databases were searched for original articles in the English language based upon the following search terms: genetic counselling, genetic testing, hereditary cancer, familial cancer, breast and ovarian cancer, colorectal cancer, *BRCA1*/*BRCA2*, HNPCC, family communication, familial risk, family disclosure, risk communication, family dynamics and duty to warn.

Additional information was obtained by performing a survey among clinical geneticists. For this study an online questionnaire was designed, based on literature data and the results of a previous qualitative interview study [5]. The survey involved all 111 clinical geneticists in the Netherlands.

A sample of 16 patients from families in which hereditary colorectal cancer or hereditary breast/ovarian cancer

was diagnosed in the previous three years was invited to participate in semi-structured interviews conducted by telephone.

Results

A short review of literature

A general advice in international guidelines is to include the issue of informing family members in the procedure of genetic counselling [6–9]. A recent report on this subject is the UK report on "Consent and confidentiality in clinical genetic practice: guidance on genetic testing and sharing genetic information" [10]. Cases in which the patient declines to inform his or her relatives have been considered in detail. Lacroix et al. [11] presented the case of a woman at high risk of breast and ovarian cancer due to a *BRCA1* mutation. This patient told her family physician that she did not want to inform her daughter while this daughter was a patient of the same physician. The authors considered the conflict of duties for the physician, the benefits and harms of non-consensual disclosure, the legal background and possible approaches to the dilemma raised.

Whereas dilemmas such as in the case presented are important, they are infrequent. A much more common problem is nondisclosure despite the fact that the patient is willing to inform family members and has started to do so. In these more common circumstances more than half of at-risk family members do not actually receive the relevant information. For example, in the Netherlands, Ramsoekh et al. [12] showed that the percentage of family members that underwent genetic testing after Lynch syndrome had been established in a proband was <50 %. One might argue that untested family members may indeed have received adequate information but subsequently chose not to undergo genetic testing. If this were true, the information process would not be considered problematic. However, numerous studies have shown that many at-risk family members will not have been informed adequately or not at all. The possible barriers that play a role in the family communication process are manifold and complex and have been reviewed by Chivers Seymour et al. [13] and Wiseman et al. [14].

Several groups have evaluated "proactive" alternatives in which the cancer register or clinical genetics centre adopts a more active role in informing family members, rather than leaving this task to the proband [15–17]. Others proposed extra efforts to support the proband in communicating information [18, 19].

Legal and ethical aspects

For the Netherlands, legal aspects of informing family members were recently outlined by Leenen et al. [20] and will be summarized here. In the considerations on genetic counselling, the question is raised concerning whether a doctor is obliged to inform family members after permission from the patient has been obtained. Importantly, there is no legal responsibility for the physician to inform relatives. The doctor has no professional relationship with family members and, practically, it would not be feasible to trace all at-risk family members. In addition, in many cases the task to inform family members would primarily be the patient's own responsibility. However, a doctor might have an obligation to inform family members in situations in which the patient will not convey the information. One cannot disregard the fact that in these cases not informing family members might be considered a breach of the doctor's professional responsibility. In contrast with the situation in some other countries, lawsuits based on a presumed duty to warn are very rare in the Netherlands.

Although a legal duty to warn has not been defined, it was considered essential that professionals clearly define their role in informing relatives, preferably in cooperation with patient organisations. A professional guideline would not only clarify what patients and family members can expect in this respect, it would also be an important reference for any legal issues that might arise.

In reviews on the ethical aspects of informing family members, most authors agree that it is primarily the responsibility of the patient to inform at-risk relatives [21–26]. Nevertheless, the clinical geneticist is also responsible for the communication of information and indeed, one generally defines a shared responsibility of the patient and doctor in this respect. The clinical geneticist should not only discuss the patient's task to inform relatives, but should also support the patient. Practically, for example, concise written information might help the patient to convey the information and lead to an improvement in the quality of the data provided. In the complex situation in which the patient does not wish to inform family members and will not permit a breach of confidentiality, confidentiality could be overruled if all efforts have been taken to receive the patient's permission without success. Therefore, in exceptional cases, the doctor might be obliged to inform relatives directly.

Survey among doctors and patients

In the survey among clinical geneticists the response rate was 58 % (64/111) and for 38 % of the geneticists cancer genetics was the main field of interest. In general, the respondents agreed with the statement that the subject of informing relatives should be part of genetic counselling. The most important reason given was a possible medical benefit for the family member and (future) offspring. However, not all geneticists considered informing relatives a task for the geneticist.

Although the majority of respondents would not reject a proactive role, many respondents emphasised that it is primarily the counselee's responsibility to communicate with family members. In their experience patients generally prefer to take on this task themselves and patients would be the best person to judge at what moment and in what way relatives should be informed. In addition, the patient would have the addresses of their relatives which would not be available to the clinical genetics centre. Moreover, respondents indicated that the clinical genetics centres would also be limited by time constraints and lack of finances.

Advantages of directly contacting family members were also mentioned. It would relieve patients for whom it might be too burdensome to inform relatives. Moreover, the information conveyed would be communicated more neutral and more accurate. Direct contact might also prevent family members from feeling obliged to undergo genetic testing for their relatives.

Eleven out of 16 invited patients and 26 of their family members from hereditary colorectal cancer or hereditary breast/ovarian cancer families participated in the survey. In general, patients and family members considered contacting at-risk relatives a duty for the patient. Patients felt that the emotional ties between family members would be a great advantage in discussing the issues involved. In their view, direct contact by a clinical geneticist might easily lead to unwarranted worries. On the other hand, patients also indicated that the actual task communicating with relatives can be very difficult. For example, if the mutation carrier is a patient with a current diagnosis of cancer, illness and treatment would make informing relatives an extra burden. Communication with family members might be an emotional burden since some relatives might not appreciate receiving information. Some patients indicated that they would not inform certain family members if they considered that the information would not be welcome. Privacy issues were also considered relevant: not all patients wished to share their diagnosis with relatives. From a practical point of view, patients mentioned that it might be difficult to obtain contact addresses of relevant family members. Moreover, it would not always be clear which family members were at risk. Due to the aforementioned reasons, support by the clinical geneticist was generally considered necessary.

Summary of recommendations included in the guideline

A series of recommendations was defined, based upon the literature review, the insights obtained from the inventories among clinical geneticists, patients, and family members, comments received from various sources as outlined above, and discussions among working group members. These recommendations are summarized below. In addition to the advice for clinical geneticists, a brochure for patients and family members was developed.

First, it is recommended that in families with hereditary or familial cancer, the subject of informing relatives is considered an integral part of the genetic counselling process, and is addressed in the first counselling session. It is important that the involvement of family members and the implications thereof are comprehensively explored by the clinical geneticist at an early stage of genetic counselling. However, a future request to inform family members should not form any barrier for the counselee to undergo genetic evaluation and advice.

Second, the primary responsibility for the communication of information lies with the counselee. To support the communication process written information for all cases of hereditary and familial cancer is to be provided, including a general brochure for patients and family members. This brochure contains background information and practical advice on how to inform family members, including the option to share the responsibility with a relative.

Third, if necessary, in cases in which relatives will not be contacted by the counselee for whatever reason, a proactive role can and should be adopted by the clinical geneticist.

The efforts in informing relatives should primarily be aimed at pedigrees with hereditary tumour syndromes. In these syndromes, the cancer risks are high and involve not only the nuclear family but also distant relatives. In contrast, in familial cancer, risks are generally limited to close relatives and these at-risk relatives will probably be informed more readily. However, not only family members predisposed for a hereditary syndrome such as Lynch syndrome should be informed, but also individuals at risk of familial syndromes, such as familial colorectal cancer.

Two kinds of letters are distinguished to support the patient in informing relatives by summarizing the condition and preventive options. In hereditary conditions such as Lynch syndrome, in addition to the summary for the referring physician and the patient, a separate "family letter" is sent to the patient to be distributed among family members. In the family letter the at-risk family members are clearly defined, thereby avoiding any misunderstanding concerning which branches of the family are at risk. The family letter should also include information on the pathogenic germline mutation identified in the family (mutation code, reference number of the laboratory involved). Contact data for the family member should also be provided. Optionally, a form for direct application for genetic counselling can be included. The family letter can be sent

by email, for easy distribution among family members, if this is in line with local regulations.

In contrast, in familial syndromes the written summary for the patient is considered to contain adequate material to inform family members.

Fourth, it is recommended that the patient should be offered support for the process of informing relatives. This support can include follow-up counselling by phone and can be performed by the clinical geneticist who has counselled the patient or, for example, a social worker. Any anticipated difficulties in informing family members will be discussed during the counselling process and suggestions for handling them provided. If these problems remain unresolved, a plan should be discussed at a follow-up session to explore ways in which additional family members might be contacted. In cases where complex family dynamics play a role, referral to a psychologist or social worker should be considered.

Fifth, the clinical geneticist can directly inform a family member after the counselee has contacted this family member and the family member has agreed to direct contact by the geneticist. Cases in which the patient cannot or is not willing to inform family members remain problematic, since now the clinical geneticist is confronted by a dilemma: there is a need for confidentiality towards the counselee, but also a responsibility may be felt towards family members. If possible, any barriers to informing family members should be removed. However, if it is impossible to inform a relative through the counselee, the clinical geneticist can and should try to inform the relative if this is considered of great importance for the health of this family member. In such an exceptional case, the counselee should be informed about the steps the clinical geneticist is taking.

Within the Dutch Society for Clinical Genetics, a committee on ethics considers ethical dilemmas in clinical genetics and also advises on individual cases. Therefore, it is recommended that complex cases should be discussed with committee members. Clearly, evaluation of the considerations made for specific cases can be useful for decision making in future cases.

Finally, for individual centres, it has been advised to set up a local protocol based on the recommendations given in the guideline.

The recommendations are schematically represented in Table 1. Note that this scheme does not request the geneticist to organise a follow-up in all cases. The working group is aware of the fact that this scheme does not ensure that all at-risk family members will be informed in all cases. However, a minimum procedure is now required and individual centres may increase their efforts for example by introducing a follow-up procedure for all cases with hereditary cancer.

Table 1 Schematic representation of recommendations on informing relatives in hereditary and familial cancer

1. At the first consultation, the possible impact of hereditary or familial cancer for family members is raised and discussed
2. In the case of a diagnosed hereditary of familial syndrome, the clinical geneticist informs the patient—supported by a written summary—on which family members are at increased risk and would benefit from receiving information
3. (a) If the patient wishes to inform these family members, the option of support is proposed. If the patient wants further support, a detailed plan is made and follow-up is planned
   (b) If the patient does not want to inform family members, the barriers involved are discussed and, if possible, removed
4. If in case 3(a) the follow-up shows that the information process is inadequate or in case 3(b) barriers cannot be overcome, the clinical geneticist directly informs family members after informing the proband about this procedure

Conclusions

The diagnosis of Lynch syndrome by the identification of a pathogenic MMR gene mutation in an affected family member is often relevant for many close as well as distant relatives. The communication of information can be a difficult task for the first family member to complete the genetic counselling procedure. Barriers in contacting family members may be psychological and/or practical. Whereas information will often be welcomed by relatives, adverse reactions may also occur. Family members may not be receptive to information, or be anxious about the impact of genetic testing. On the other hand, failure to communicate information and occurrence of disease in relatives who were not informed may also complicate family relationships.

Since notifying relatives is recognised both by patients and clinical geneticists as an essential procedure in the framework of genetic counselling, one should not rely on inadequate methods of conveying the information. The guidelines discussed in this article were developed to overcome acknowledged barriers. However, several limitations also have to be acknowledged. Not all at-risk family members are known to patients or geneticists, and not all known at-risk family members can be informed, for example if addresses are unknown. For clinical genetics centres, there may be limitations in maximising efforts to inform all known at-risk relatives. Some centres may choose to organise follow-up for all families with hereditary and familial cancer, while other centres may adhere to the minimum requirements for follow-up as defined in the guideline.

The existence of a new guideline does not automatically imply that the recommendations will be implemented in clinical practice. Most guidelines need well-developed, well-executed and sustained implementation programmes

[27]. Due to the complexity of the problem, the new guideline described here will probably not lead to a fast and dramatic improvement in informing relatives. However, implementation of the guideline outlined in this article may be facilitated by involvement of both target groups—patients and doctors—in the development of the guideline, the inclusion of a brochure for patients and family members, the obligatory setting-up of local protocols for clinical genetics centres, and evaluation of these protocols in audit programmes.

The delineation of the legal aspects is likely to help clinical geneticists in adopting a position in the unusual cases in which the patient is not willing or able to contact family members.

Studies aimed at further analysis of barriers in communication and ways to overcome these barriers, for example by support programmes for patients or programmes aimed at a more proactive approach of family members by clinical geneticists may lead to evidence-based guidelines in the future.

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